Original Article

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ROLE OF PRE-INCISION, INTRAVENOUS PROPHYLACTIC AMIODARONE TO CONTROL ARRHYTHMIAS IN PATIENTS WITH RHEUMATIC VALVULAR HEART DISEASE UNDERGOING MITRAL VALVE REPLACEMENT

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ABSTRACT

Objective: To evaluate the effect of intra- operative single intra venous dose of amiodarone on post operative cardiac arrhythmias in patients undergoing valvular heart surgery.

Study Design: Randomized controlled trials.

Place and Duration of surgery: This study was performed at Armed forces Institute of Cardiology Rawalpindi form Jan 01, 2011 to Dec 31, 2011.

Patients and Methods: In this study 80 patients with rheumatic valvular heart disease and undergoing elective mitral valve replacement were randomly divided into two groups. Group I, n =40 (Amiodarone group) was given single intravenous dose of amiodarone (5 mg/kg in 100 ml of saline over 30 min) before sternotomy incision. Group II, n=40(control/placebo group) was given 100 ml of saline over 30 min.

Result: In the amiodarone group, after removal of aortic cross clamp 75% patients had sinus rhythm compared to 47.5% in control group. *p*=0.045. Similarly 15% had AF, 5% JR and 5% VT/VF in amiodarone group in contrast to 32.5% with AF, 12.5% JR and 7.5% Vt/VF in control group. (*p*=0.045). Response to cardioversion was positive in 75% of the patients requiring shocks in amiodarone group as against 43.75% in the control group. (*p*=0.044).

Conclusion: A single intravenous bolus dose of amiodarone is effective in decreasing the incidence of cardiac arrhythmias after mitral valve replacement in patients with rheumatic MVD.

Keywords: Rheumatic valvular heart disease, amiodarone, cardiac arrhythmias, Atrial fibrillation, cardio version.

INTRODUCTION

A common cause of atrial fibrillation (AF) in developed world is elderly age but in developing countries like Pakistan the predominant cause is rheumatic mitral valve disease. AF is associated with increased thromboembolic complications (17-18%) and decreased cardiac output[1,2]. The presence of AF after mitral valve replacement is associated with worse New York Heart Association Class (NYHA) and increased transmitral gradients[3]. Maintenance of normal sinus rhythm is superior to ventricular rate control in patients with rheumatic AF with respect to effects on exercise capacity, quality of life, morbidity and possibly mortality[4]. According to a study, mitral valve surgery restored normal sinus rhythm only in 8.5% of the patients with chronic AF[5]. Technical advances in surgery and anesthesia, as well as changing methods of myocardial protection, have not decreased the incidence of postoperative atrial tachydysrythmias[6,7]. AF is facilitated by atrial manipulation, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances and electrophysiological changes that accompany sympathetic nervous system discharge[8] and these factors are common in valvular heart surgery.

Many drugs have been tried to prevent this common postoperative complication. As sympathetic activation may be important in the pathogenesis of atrial fibrillation after coronary artery bypass grafting, ß-adrenoceptor blockade is considered good choice for prophylaxis. Propranolol, Metoprolol, Atenolol and Acebutolol have been found to be successful in this regard.

The preoperative use of intravenous magnesium sulfate dramatically reduces the incidence of atrial fibrillation after cardiac surgery[9]. Patients who are prophylactically

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digitallized prior to coronary artery bypass grafting have relatively low incidence of atrial fibrillation afterwards[10]. Amiodarone has shown most promising results among all anti arrhythmic drugs with successful conversion and maintenance of normal sinus rhythm in 50-70% of the patients[11]. Amiodarone is a unique drug belonging to class III anti dysrhythmic agents. It is being used for the treatment of supra ventricular, ventricular and acute myocardial infarction related dysrhythmias. The use of low dose intravenous as well as oral amiodarone for 3-5 days before and then after the coronary artery bypass grafting has significantly reduced the development of atrial fibrillation[12,13]. Oral amiodarone ,in addition to slow onset of action requires admission of the patient or repeated outpatient visits to monitor the patient. Taking into consideration the rapid onset of the intravenous amiodarone[14] few studies have been conducted abroad to observe its effects on post cardiac surgery AF. In Pakistan, very scarce data is available on effect of prophylactic intravenous amiodarone on post rheumatic valvular replacement arhythmias. In our study we studied the effects of an IV prophylactic bolus (5 mg/kg) dose of amiodarone on patients with rheumatic mitral valve disease (MVD) undergoing MVR. Hypothesis of our study was that prophylactic IV bolus of amiodarone may be preventive and or curative for arrhythmias after rheumatic mitral valve replacement.

PATIENTS AND METHODS

These randomized controlled trials were performed at Armed forces Institute of Cardiology Rawalpindi form Jan 01, 2011 to Dec 31, 2011. It was a prospective, interventional, case control study. Protocol of study was approved by hospital ethics committee. The patients of either sex with ASA I-III, age between 20-60 years, having rheumatic mitral valve disease with or without arhythmia, undergoing elective mitral valve replacement on cardiopulmonary bypass were included in the study. The patients were excluded from the study if they had been taking amiodarone or any other antirhythmic drugs of class I, III, IV during last six months or allergic to amiodarone. Similarly pregnant patients, thyrotoxic, with elevated liver enzymes, renal dysfunction (serum creatinine >2 mg/dl), with heart rate less than 50 beats per minute and those with NYHA class IV were excluded from the study. This study was performed on 80 patients after written informed consent. All the patients completed the study. Patients were randomly divided into two groups using envelope method. Group A was given amiodarone (5mg/kg in 100 ml saline via burrette), while group B (Control group) was given 100 ml saline as placebo. The burettes were prepared by the anaesthesia assistant who was not involved in the administration of drugs to the patient and data collection. While the attending anaesthetist and ICU staffs were not aware of which burette was administered to the patient as burettes were covered.

The same anaesthetic technique was used in all patients. Pre medication was offered in the form of oral Lorazepam 1-2 mg depending upon weight, and intra muscular nalbuphine 0.1 mg/kg and promethazine 0.3 mg/kg, one hour before the surgery. All preoperative drugs except antiplatelets, digoxin and diuretics were continued till the morning of the surgery day. Induction of general anaesthesia was done with intravenous midazolam 0.05 mg/kg, fentanyl 1 ug/kg and propofol 1mg/kg. Intubation and muscle relaxation was facilitated by the use of pancuronium bromide. Anaesthesia was maintained with oxygen, air, isoflurane and fantanyl. Amiodarone or placebo were administered after induction of anaesthesia but before sternotomy incision over 30 min. If any patient developed hypotension, it was treated with volume resuscitation and dobutamine if required, similarly bradycardia was treated with atropine 0.01 mg/kg.

All surgeries were performed under hypothermic cardiopulmonary bypass (cooling to 28^{o}C), using ante grade warm blood cardioplegia, non-magnesium containing prime and a membrane oxygenator. Cardioplegia was

repeated after every 20 minutes. Surgical technique was almost same. Blood glucose levels were maintained between 110-140 mg/dl and serum potassium levels were maintained between 4.5-5.0 meq/l as per department protocol. All patients were rewarmed to 37^{o}C. Magnesium sulphate 30 mg/kg was administered through CPB pump after removal of cross clamp to every patient as per department protocol.

After removal of aortic cross clamp, cardiac rhythm was observed. If there was ventricular tachycardia or ventricular fibrillation and it did not respond to the bolus of magnesium sulphate and optimization of acid base status and electrolytes, internal defibrillation with energy ranging from 10-40 J was done. If the patient had heart rate < 50 beats per min epicardial pacing with AAI or VVI mode was started. In cases with atrioventricular block, dual chamber sequential pacing was started. Dobutamine/ adrenaline was started if hypotension (systolic BP < 90mm Hg) persisted due to poor contractility of heart inspite of adequate preload. After successful weaning from CPB and reversal of heparin as per department protocol, patients were surgically closed and shifted to post operative surgical ICU where they were monitored for any arhythmia for 48 hours and treated as per ICU protocol.

The end points of the study in ICU for analysis were, an episode of arhythmia lasting for at least 5 minutes, number and energy of shocks required, response to cardioversion, episodes of haemodynamic instability (systolic BP < 90 mmHg), requirement of an antiarrhythmic drug and requirement of additional ionotropic support.

The statistical analysis was performed by SPSS version 17. Descriptive statistics were used to describe the results i.e. mean and standard deviation (SD) for quantitative variables while frequency and percentages for qualitative variables. Quantitative variables were compared through Independent samples' t – test for normal variables and through (Mann-whitney) U test for non-normal variables while qualitative variables were compared using chi-square test between the two groups. *p*-value < 0.05 was considered as significant.

RESULTS

Eighty patients were enrolled and randomized into two groups, (Group I (n=40) received Amiodarone) and (Group II (n=40) received saline as placebo) in this study. All patients completed the study and underwent intraoperative and post operative monitoring and assessment. There was no significant difference in the patient characteristics, co morbidities,other demographic profile, anaesthetic technique, type of procedure, bypass time, aortic cross clamp time and type of prosthetic valve used in two groups as shown in the table 1.

The difference of developing hypotension and bradycardia was insignifiacant between two groups. This hypotension and bradycardia was successfully managed by slowing of the amiodarone infusion, volume resuscitation and atropine 0.5-1.0 mg.

On removal of the aortic cross clamp, among patients in group I, there was significantly low frequency of developing, atrial fibrillation, junctional rhythm and VT/VF as compared to group II. *p*= 0.045

Even after correction of electrolytes, acid base balance, bolus of magnesium sulphate (30 mg/kg) and bolus of lignocaine (1.5 mg/kg) many patients with arhythmia in both groups required cardioversion. Response to cardioversion was significantly more in group I, (*p*= 0.044). Similarly energy level required and number of shocks required were significantly less in group I as compared to group II as shown in the table-2. The requirement of pacing was insignificant between the two groups. Need for an ionotrpe was almost same in both groups (Table-2).

At the end of surgical procedure and before shifting to ICU significantly higher number of

patients had AF and junctional rhythm in group II as compared to group I (p = 0.008).

During first 48 hours of post operative period there was significantly higher frequency of developing arrhythmia in group II as compared to group I (p=0.029).

In group I, patients' response to cardioversion was significantly higher as compared to group II, (p=0.019). Similarly the energy level required and numbers of shocks required were significantly less in group I as compared to group II (p=0.039)(Table-3). During first 48 hours antirhythmic drug was required for only 3 patients in group I as compared to 12 patients in group II (p=0.01) (p=0.171).

The difference in the incidence of postoperative complications like bleeding, reopening, wound infection, chest infection, prolonged ventilation and death remained insignificant between two groups (Table-3).

At the time of shifting from ICU, 7.5% patients in amiodarone group had arrhythmia that was mainly atrial fibrillation as compared to 25% patients in saline group. (p = 0.034).

Table-1: Comparison of demographic data of group I (Amiodarone) and group II (Placebo).

Variable	Group I, n= 40 (Amiodarone)	Group II, n= 40 (Placebo)	p- value
Age	39.32+10.23	39.07+10.16	0.645
Sex (male: female)	21:19	17:23	0.377
Height (cm)	159.87+ 6.63	158.87+ 5.90	0.479
Co morbidities			
Diabetes mellitus	14 (35%)	12 (30%)	0.638
Hypertension	15 (37.5%)	13 (32.5%)	0.644
Smoking	11 (27.5%)	12 (30%)	0.808
Left ventricular function (EF)	51.12 + 5.81	50.20 + 5.45	0.465
NYHA Class			
Class II	21(52.5%)	22 (55%)	0.825
Class III	19 (47.5%)	18 (45%)	
Type of MVD			
MR	2 (5%)	3 (7.5%)	
MS	25 (62.5%)	25 (62.5%)	0.904
Mixed	13 (32.5%)	12 (30%)	
Number of patients in AF before surgery	16 (40%)	17 (42.5%)	0.823
Type of Prosthetic valve			
Mechanical valve	30 (75%)	32 (77.5%)	0.598
Tissue Valve	10 (25%)	8 (20%)	

NYHA : NewYork Heart Association, EF : Ejection fraction, MVD : Mitral valve disease.
MR: Mitral regurgitation, MS : Miral stenosis, AF: Atrial fibrillation

DISCUSSION

Arhythmias after cardiac surgery are associated with increased risk of complications, length of stay and cost of care. AF occurs in 20-65% of patients after cardiac surgery on cardiopulmonary bypass[15]. The incidence is higher in patients undergoing valve surgery or combined CABG-valve surgery[15]. The potential complication of AF includes haemodynamic compromise in immediate post operative period. Hence the use of concomitant antiarhythmic procedure or medication is recommended in patients undergoing valvular procedures under cardiopulmonary bypass[5]. The principle cause of arhythmia is related to large atrial size[16]. Recent

data suggest that inflammatory infiltration of myocardium predisposes to AF[17]. Atrial damage has been associated with post operative AF[18] but perioperative inflammation following cardiac surgery/CPB has recently been noted to be responsible for postoperative AF[17].

logical. Our study represents a trial to find out if a single pre CPB intravenous bolus dose of amiodarone decreases the incidence of arhythmias after mitral valve replacement in patients with rheumatic mitral valve disease with or without AF.

Table-2: Comparison of intra operative data of group I (Amiodarone) and group II (Placebo).

Variable	Group I, n= 40 (Amiodarone)	Group II, n= 40 (Placebo)	*p*-value
*Patient developing hypotension during drug administration	5 (12.5%)	1(2.5%)	0.093
Patients developing bradycardia during drug administration	6 (15%)	1(2.5%)	0.051
Cardiopulmonary bypass time(min)	78.20 + 8.22	78.70 + 8.47	0.790
Aortic cross clamp time (min)	54.82 + 8.97	54.80 + 9.03	0.990
Rhythm after cross clamp removal Sinus Rhythm AF JR VT/VF	 30 (75%) 6 (15%) 2 (5%) 2 (5%)	 19 (47.5%) 13 (32.5%) 5 (12.5%) 3 (7.5%)	0.045
No of patients responding to cardioversion	6/8 (75%)	5/16 (31.35%)	0.044
No of shocks required	1.75 + 0.88	2.65 + 0.60	0.026
Energy level required in joules	20.00 + 10.35	27.94 + 6.62	0.029
Patients requiring ionotrpes	25 (62.5%)	29 (72.5%)	0.346
Patients requiring pacing	13 (32.5%)	11 (27.5%)	0.631
Rhythm at the end of surgery Sinus Rhythm AF JR	 37 (92.5%) 3 (7.5%) 0	 28 (70%) 10 (25%) 2 (2.5%)	0.008

AF : Atrial fibrillation, JR : Junctional rhythm, VT : Ventricular tachycardia.
VF : Ventricular Fibrillation, * Systolic BP<90 mmHg > 5 min inspite of adequate preload (CVP = 8-10 cm of H_2O) , @ Heart rate < 50 beats/min

Several meta-analyses have shown amiodarone to be effective in reducing the incidence of AF and its complications after CABG alone or combined CABG and valvular surgery[19,20]. Onset of antiarrhythmic effect of oral amiodarone takes 7-10 days. Complete antiarhythmic effect may not be noticed for upto 10 weeks. However the onset of antiarhythmic effect of intravenous amiodarone is rapid. So the use of intravenous amiodarone as a prophylaxis to post valvular surgey arhythmias is more

Prophylactic oral amiodarone has been shown to reduce the incidence of AF following open heart surgeries[11,21,22] but there are few studies to show the role of single intravenous, pre-CPB dose of amiodarone to reduce the incidence of post valvular heart surgery arhythmias. Selveraj et al[23] evaluated the effect of single intra operative single dose intravenous amiodarone to convert AF in sinus rhythm in patients undergoing valvular heart surgery. AF was observed in 14.3% of the patients in the

amiodarone group and 37.5% of the patients in control group, *p* value 0.035. Seventy three percent of the patients in the amiodarone group and 47.5% patients in the control group reverted to SR after cardioversion. The dose of amiodarone used was 3 mg/kg and all of the patients included in this study had AF for one year with rheumatic valvular heart disease. In another study by Beaulieu et al.[24] using intravenous dose of 300 mg of intravenous bolus amiodarone in the operation theatre followed by infusion of 15 mg/kg/24 hr for 2 days did not reduce the incidence of post valvular AF. There was a trend of reduction in AF during drug administration but arhythmia recurred after stoppage of drug. However this is not unexpected of the small trials. Amr et al[25] evaluated effect of amiodarone 3 mg/kg on patients of valvular heart disease without AF who underwent valvular surgeries on CPB. Like our study this study showed positive effect of amiodarone group regarding post cross clamp removal arrhythmias, response to cardioversion and incidence of AF in first 5 days postoperatively. It should be noted that this study included only those patients who had no previous AF. In our study we tried amiodarone in a dose of 5 mg/kg and our patient population was both with and without AF. All of the patients had mitral valve disease and underwent mitral valve replacement either with mechanical or tissue prosthetic valve while in previous studies patients having different valve involvements and valve repairs were also included. We monitored

Table-3: Comparison of post operative ICU data of group I (Amiodarone) and group II (Placebo).

Variable	Group I, n= 40 (Amiodarone)	Group II, n= 40 (placebo)	*p*- value
Arrhythmia in first 48 hours			
AF	5 (12.5%)	14 (35%)	
JR	1 (2.5%)	0	0.029
VT/VF	1 (2.5%)	1 (2.5%)	
Response to cardioversion	3/6 (50%)	2/15 (13.3%)	0.081
No of Shocks	2.00 + 0.89	2.73 + 0.59	0.039
Energy level required in joules	108.33 + 58.45	160.33 + 33.804	0.019
Requirement of antirrhythmic drug	3 (7.5%)	12 (30%)	0.01
*Episodes of haemodynamic instability	2 (5%)	7 (17.5%)	0.079
Additional Ionotrope required	1 (2.5%)	4 (10%)	0.170
Patients requiring pacing	4 (10%)	1 (2.5%)	0.171
Ventricular rate during first 48 hours	73.27 + 10.56	80.55 + 8.61	0.001
Other complications			
Bleeding	2 (5%)	2 (5%)	
Reopening	1 (2.5%)	1 (2.5%)	
Wound Infection	3 (7.5%)	1 (2.5%)	
Chest infection	1 (2.5%)	1 (2.5%)	0.162
Prolonged vent	2 (5%)	2 (5%)	
Death	0	0	
Rhythm at the time of shifting from ICU			
AF	3 (7.5%)	10 (25%)	0.034
JR	0	0	

AF : Atrial fibrillation, JR : Junctional rhythm, VT : Ventricular tachycardia.

our patients for 48 hrs in ICU for any kind of arrhythmias. Although there was significant increase in the incidence of hypotension and bradycardia during drug administration but it was successfully managed by fluid resuscitation and atropine. Otherwise amiodarone was found to be significantly effective to reduce the incidence of post aortic crossclamp removal arrhythmias. The response to cardioversion was increased and requirement of energy and number of DC shocks decreased as compared to control group. Our results are comparable to previous studies however we did not study the recurrence of arhythmias after shifting from ICU. Other limitations included; small sample size, uncontrolled preoperative antiarhythmic drugs and non measurement of blood amiodarone levels.

CONCLUSION

It is concluded that an intravenous prophylactic amiodarone bolus is effective in cure of and prevention of arrhythmias following mitral valve surgery in patients with MVD with or without AF. The dose of amiodarone 5 mg/kg is well tolerated and more effective in this regard.

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